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Quinolones in Community-Acquired Pneumonia; Are They Born Equal?

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Abstract

There has been debate on the best treatment regimen for CAP, whether to start treatment with β-lactams, β-lactam β-lactamase inhibitor, macrolides, a combination of the earlier or quinolones, among other less commonly used agents. In this review, an attempt to examine some data on the utilization and importance of respiratory quinolones in the treatment of CAP, and to examine whether quinolones are the same in clinical and microbiological efficacy, shall we stick to seven days of treatment versus shorter duration without compromising outcome? Are resistance patterns for respiratory quinolones the same, and are there savings associated with using some respiratory quinolones over others? Moreover, are there any differences in mortality when examined as a treatment end-point, and if there is any differences in speed of recovery for different respiratory quinolones? Do we need to incorporate pharmacokinetics/pharmacodynamics principles in the treatment of CAP, and how to dose anti-infective agents in CAP, opposed to leaving treatment-doses for minimum inhibitory concentration alone?

Key words: CAP, Quinolones, PK/PD, quinolones resistance, fluoroquinolones,

Introduction

Community acquired pneumonia conventionally classified into three severity levels: outpatient pneumonia, non-ICU in-patient pneumonia and ICU-pneumonia. Microorganisms that are prevalent in the three severity levels are Streptococcus pneumoniae and Hemophilus influenzae, meanwhile Mycoplasma pneumoniae, Chlamydophila pneumoniae and respiratory viruses add to the outpatient CAP. Staphylococcus aureus and gram–negative bacilli contribute as a major burden in ICU-CAP, while inpatient non ICU-CAP to a large extent shared by aspiration microorganisms and legionella species, the later contributes as well to ICU-CAP. (1)

Resistance among respiratory pathogens has been escalating; Streptococcus pneumoniae harbors penicillin resistance, and has been increasing, where lately isolates from several studies showed absolute resistance between 14.6-21.5% with intermediate resistance of about 12.7 - 17.9%. (2) Arab countries share the same phenomena of high resistance patterns among pneumococci, where in Kuwait 55% of pneumococci were penicillin-resistant (intermediate 46% and full 9%). Fourty-one percent were sulfamethoxazole-trimethoprim-resistant, 9% resistant to cefotaxime and ceftriaxone, 15% to amoxycillin-clavulanate, 17% to cefuroxime, 77% to cefaclor, and 14% to clindamycin. In United Arab Emirates the quinolones ofloxacin- and ciprofloxacin-resistant pneumococci were reported, in addition to penicillin- and cephalosporins-resistant strains. In Yemen, Egypt, Qatar and Saudi Arabia penicillin-resistant pneumococci also widely range in their susceptibility patterns from 8 - 78%. In some African countries, pneumococcus penicillin resistance is about 50% and up to 80% in Japan, penicillin resistant pneumococci acquire other antimicrobials' resistance like macrolides resistance. Moreover, pneumococci show multiple resistance patterns against antimicrobials. (2, 3, 4, 5,)

H. Influenzae used not to harbor significantly β–lactamases in clinical specimens before 1972; lately, β-lactamases contribute to large burden in Hemophilus. (6) Resistance in H. influenzae to many antimicrobial agents increased dramatically, with increased MIC's from 0.25 - 0.5 µg/ml in the pre β-lactamases era to over 32 mg/l in the post β-lactamases era, ampicillin susceptibility dropped to about 70% and TMP-SMX to less than 80% susceptibility. Hitherto, quinolones maintain excellent susceptibilities toward respiratory pathogens, namely gemifloxacin which demonstrates impressive low MIC's against clinical isolates of Streptococcus pneumoniae (MIC_{90} = 0.016 – 0.06), Hemophilus influenzae (MIC_{90} < 0.0008 – 0.06), Moraxella catarrhalis (MIC_{90} = 0.008 – 0.3), Chlamydia pneumoniae (0.25) and Legionella spp. (0.125). (6, 7, 8)

Diagnosis

Due to the changing resistance patterns in respiratory pathogens, diagnosing the infecting pathogen is of utmost importance in approaching CAP, this holds true for all risk categories, especially those with severe illnesses like ICU-CAP, failure of previous antimicrobial regimen, cavitary infiltrate, leucopenia, COPD, asplenia, recent travel, active alcohol abuse and patients with pleural effusion. (9) In spite of that, the recovery of suspected respiratory pathogens e.g. pneumococcus in adults' sputum with CAP has been decreasing. Though examining expectorated sputum is a simple diagnostic procedure, nevertheless its benefit in revealing a diagnosis, when properly processed is up to 70%, especially in CAP due to S. pneumoniae, S. aureus , S. pyogenes , H. influenza and gram-negative bacilli, an organism obtained from sputum correlates with the diagnosis in 93% of times. (10) Other diagnostic methods may be used safely mostly in inpatient CAP, like trans-thoracic needle aspiration which is disfavored by practicing physicians and patients, bronchoscopy though it is uncommonly used in CAP, but it is helpful, especially when it is used with protected brush specimen using culture of threshold 10^3 CFU /ml . Other diagnostic tests of great help are urinary antigens detection, where it helps in diagnosing CAP due to legionnairs disease that accounts for about 2 - 6 % of CAP in some countries, pneumococcal antigen may be used, though its sensitivity and specificity are less in patients with non-bacteremic CAP. The need to have an accurate microbiological diagnosis in CAP is compelling because studies clearly showed that pathogen-directed treatment was superior to empiric treatment when mortality was measured as an endpoint, as well as length of hospital stay and clinical failure. (10, 11)

The Quinolones

Quinolones are useful anti-infective agents, with wide scale acceptance among physicians for their spectrum against respiratory bacteria, easiness of administration and lower side effects profile compared with other antimicrobials, their use has been increasing over the last decades in patients 18 years or older. On the other hand, like other antibacterial agents, the potential of some respiratory bacteria to develop quinolones resistance is there, seeing that ciprofloxacin use escalates. Prevalence of ciprofloxacin-resistant strains increased over years in many parts of the world, with increased degrees of resistance i.e. higher in prevalence and with higher MIC's, though it remained low when compared with other anti-infective classes. (12, 13)

Quinolones nucleus modification gave rise to new agents, with variable PK/PD and antimicrobial properties, this lead to their classification into four generations for a better understanding. Quinolones are classified into four generations based on their in vitro activity; first generation that include parent compound of limited clinical use such as nalidixic acid, second generation; include popular agents used for many infections i.e. ciprofloxacin, levofloxacin and ofloxacin; the third generations like sparfloxacin, gatifloxacin and grepafloxacin, and the fourth generations like moxifloxacin, gemifloxacin and trovafloxacin. (14)

Since their introduction in the late 1990's respiratory quinolones demonstrated their benefit by clearly showing that their 30-days-mortality is less than other agents used in the treatment of CAP, like β-lactam/β-lactamase-inhibitor plus macrolide or an aminoglycoside plus another agent. The second-generation cephalosporins plus macrolides, and non-pseudomonal third-generation cephalosporins plus macrolides almost has similar effect on the 30-days-mortality like quinolones mono-therapy (**Figure 1**). Adjusted mortality among patients initially treated with respiratory fluoroquinolones and the other two regimens became significantly lower beginning 2, 3, and 7 days after hospital admission, respectively. (9, 15, 16). A number of international recommendations for CAP treatment were published over the last years e.g. IDSA guidelines, where respiratory fluoroquinolones are recommended among first-line agents; like in outpatient CAP, or as first line agents as in inpatient non-ICU CAP, and as first agent in previous both categories when patients are β-lactam allergic. In severe ICU-CAP requiring admission, ciprofloxacin and levofloxacin are the preferred agents. On the other hand, in the British Thoracic Society guidelines for 2009 discourages the use of respiratory quinolones as first line treatment choice in favor of amoxicillin/clavulanate, because of increased incidence of MRSA and CDI associated with their excessive use, and because RFQ were found as good as other agents in low severity CAP. (17)

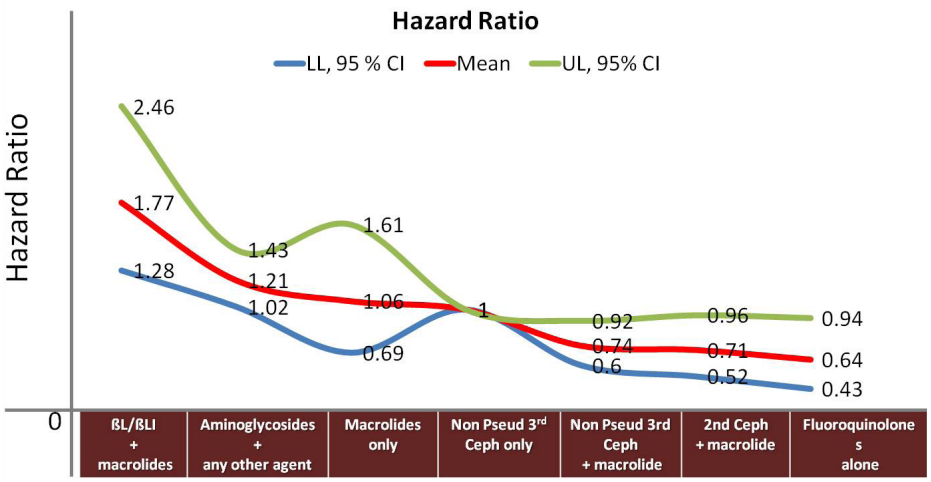

Figure 1. Independent associations between initial antimicrobial therapy and 30-day-mortality among different antimicrobial regimens used for the treatment of CAP. Third generation non-pseudomonal parenteral cephalosporins used as a reference to calculate hazard ratios and assigned a ratio of one. The middle curve is the hazard ratio with the other two lines for 95% Confidence Interval. (Adapted from reference 16)
LL: lower bound for the confidence interval
UL: upper bound for the confidence interval
βL/βLI: beta-lactamase, beta-lactamase inhibitor

Adherence to guidelines is encouraged as the total management-related effect is in its favor, though in a study, it showed increased utilization of chest X-rays, increased prescription of antimicrobials with relatively less diagnosis of CAP. Adherence to guidelines showed in a study of 780 patients from Barcelona favorable effects that outweigh some previous caveats; it clearly showed decrease in mortality (p = <0.001) and decrease in length of hospital stay (p = 0.004). Bearing in mind that guidelines on CAP treatment should be considered with the prevalent microorganism and susceptibility trends for each part of the world; it is important to be familiar with local resistance patterns, and microbiology results, all should be used to narrow the choice of suitable antimicrobials. (16, 18, 19)

Quinolones; MIC's and resistance

Quinolones are potent agents, against bacteria encountered mostly in lower, as well as upper respiratory infections, with low MIC's. The fourth generations RFQ are the most potent agents among quinolones in activity against pneumococci, and other respiratory pathogens. The least effective quinolone is ciprofloxacin where susceptible pneumococci have relatively elevated MIC's, and they rank highest for resistance in pneumococci, about 1,8%, though resistance detected rarely among RFQ's, but in levofloxacin is about 0.7%, gatifloxacin 0.6%, and the least is for moxifloxacin and gemifloxacin where resistance prevalence is 0.3% and 0.1% respectively. (20, 21)

The activity of RFQ's are not affected by pneumococci patterns of penicillin resistance, whether susceptible, intermediate or resistant. On the other hand, these patterns adversely affect susceptibilities and cause elevated MIC's among macrolides and β-lactams, which may make them clinically not useful to a large extent. Challenging RFQ's against ciprofloxacin-resistant pneumococcus strains showed that the fourth generation RFQ still maintain low MIC's compared with the second generation RFQ like levofloxacin. (22) Furthermore, testing levofloxacin-susceptible (**Figure 2A**)and levofloxa-

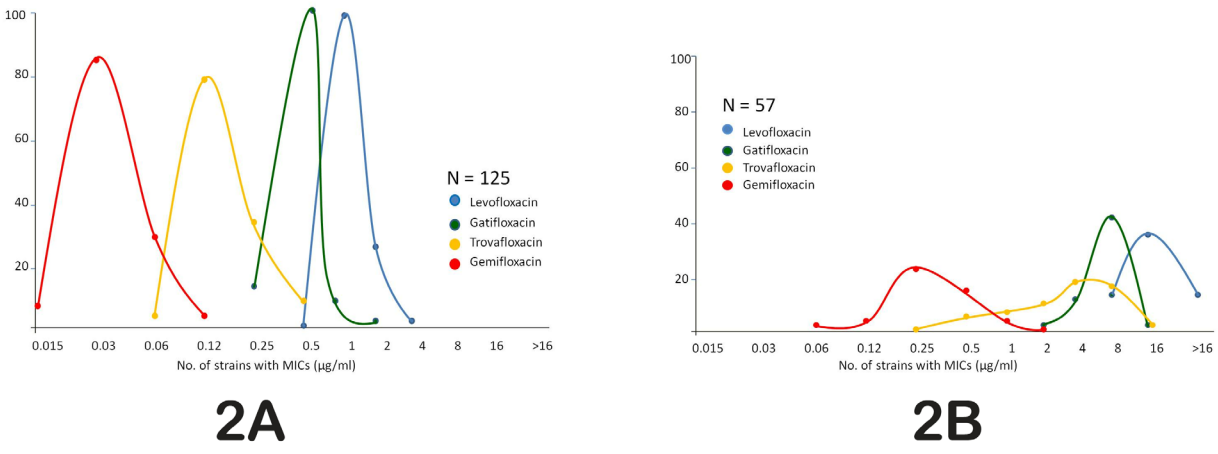

Figure 2. Comparative activities of four fluoroquinolones against (**A**) levofloxacin-susceptible S. pneumoniae clinical isolates and (**B**) levofloxacin-resistant S. pneumoniae clinical isolates. (Adapted from reference 23)
MIC: minimum inhibitory concentration N: number of tested pneumococci.

cin-resistance (**Figure 2B**) pneumococci against other RFQ showed clearly that gemifloxacin and clinafloxacin are the most potent agents maintaining low MIC's in pneumococci, and adequate clinical effect on those levofloxacin-susceptible and -resistant pneumococci (MIC ≥ 8 µg/ml). In this regard, levofloxacin-resistant pneumococci do not preclude using gemifloxacin and clinafloxacin in their treatment, considering the other overall data on both agents are available, like their PK/PD and clinical use studies, as is the case with gemifloxacin. (23)

Resistance and its evolution among RFQ

Streptococcus pneumoniae acquire resistance against quinolones through mutations in the genes encoding for the target enzymes (topoisomerases) located in quinolones resistance determining region (QRDR) with genotypes gyrA, gyrB, parC, and parE; resistance occur in these loci when amino acids substitution occur at different loci. The "first-step" occur when pneumococci acquire parC mutation (topoisomerase IV) which occurs fairly frequent (~$1/10^7$ of pneumococcal colonies), this acquisition increases resistance to about four-folds in levofloxacin MIC, and this occurs when pneumococci come under ciprofloxacin-exposure pressure. Higher MIC's occur and resistance worsen should a second-step mutation occurs in another active site i.e. gyrA (topoisomerase II). When combined parC and gyrA occur, resistance to gatifloxacin, levofloxacin and trovafloxacin become at or above resistance breakpoints defined by CLSI, but not to gemifloxacin and clinafloxacin, gemifloxacin with its marked potency against wild type and quinolone-resistant mutants may ensue from greatly stabilizing the cleavable complexes with the target enzymes, and possibly clinically evident. Resistance may occur to a lesser extent through mutations in parE and gyrB, resistance can also be mediated by active efflux, although its role in contributing to resistance in the newer RFQ's is unclear. (2, 23, 24, 25)

Each step in resistance evolution diminishes quinolones susceptibility by 4-8 folds among pneumococci. Consequently, if one quinolones MIC was lower than the other as it occur in e.g. levofloxacin compared with ciprofloxacin respectively, then one mutation may put ciprofloxacin at or above susceptibility zone, while levofloxacin maintains its potency against pneumococci, unless more than one mutation occur. However another pattern of quinolones resistance occurs, when pneumococci acquire one-step mutation with elevation in MIC, this will not affect some quinolones, like gemifloxacin and clinafloxacin. Other agents may suffer from more than one mutation, thus come in the full resistance zone. Depending on quinolone potency, number and type of mutations in pneumococci may acquire; resistance may assume a cross-resistance or divergent (dichotomous) patterns. (26)

This phenomena may be helpful in explaining the inclusions of mutants, and prevention of resistance by some potent quinolones, referred to as mutant prevention concentration. Quinolones that may account for mutants coverage in their spectrum are the fourth generation RFQ, where restriction for mutant selections was found most potent in gemifloxacin followed by moxifloxacin then trovafloxacin, gatifloxacin, grepafloxacin and the least with levofloxacin. (27, 28, 29, 30, 31)

In an elegant trial carried out by M. Ryback and colleagues, the potential for resistance development were tested for gatifloxacin, gemifloxacin, levofloxacin and moxifloxacin (**Figure 3**). For that purpose, he designed a simulation model, keeping in a compartment $10^{8.5}$ –10^9 $\log_{10}$ CFU/ml of Streptococcus pneumoniae ATCC 49619 and BSP2443, both strains did not have mutations for quinolones resistance in the QRDR's i.e. no parC, parE, gyrA and gyrB as well as no efflux mechanism for resistance. Antimicrobials were infused into the compartment to simulate the pneumococcal target *f*AUC/MIC. Free quinolones (protein unbound) levels in the compartment was calculated based on manufacturers' recommendations for quinolones protein binding (20% for gatifloxacin, 60% for gemifloxacin, 30% for levofloxacin and 40% for moxifloxacin). Within duration of up to 96 hours, pneumococcal strains were constantly exposed to each quinolone independently. It was found that the evolution of resistance was observed to start earlier in levofloxacin model and progressively increased, thus, leading to a significant difference in the evolution of pneumococcal resistant mutants in comparison with the other quinolones e.g. moxifloxacin ($p = 0.0001$), gemifloxacin ($p = 0.001$) as well as gatifloxacin ($p = 0.001$). Ryback and colleagues concluded that clinical doses of gatifloxacin, gemifloxacin, and moxifloxacin exceed the *f*AUC/MIC resistance breakpoint against wild-type pneumococci and that the exposure breakpoints differ among levofloxacin, gatifloxacin, gemifloxacin, and moxifloxacin. Consequently, in the prevention of resistance, moxifloxacin = gemifloxacin > gatifloxacin > levofloxacin. This may be due to different structures quinolones have within the same class. (38)

Pharmacokinetics/Pharmacodynamics of quinolones

Dr. Harry Eagle started in the nineteen-forties to -fifties the concept of pharmacokinetics/pharmacodynamics (PK/PD), but his work was not appreciated until many years later. From the late 1970s through the early 1990s, PK/PD concepts were rediscovered and expanded upon thorough elegantly designed rodent experiments conducted by Dr. William Craig. (32) Our understanding of PK/PD largely improved in the last few decades; types of bacterial killing came from work on mice models, later translated and studied in humans. Several types of bacterial killing was recognized; time-dependent which

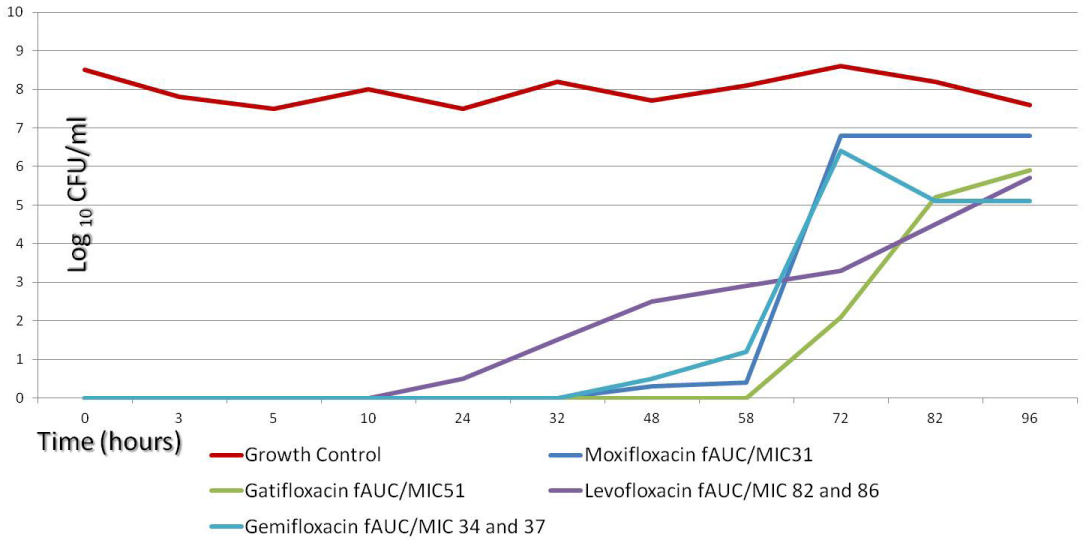

Figure 3. Schematic representation of the four tested quinolones in a simulation model to assess the induction of resistant mutants by continuously exposing pneumococci up to 96 hours. Pneumococci were exposed to antimicrobials concentrations as recommended by the manufacturer based on protein binding. The complimentary non-resistant curve for each quinolone-induced mutant curve is not showing here for simplicity. (Adapted from reference 38)
*ƒ*AUC: free area under the curve
MIC: minimum inhibitory concentration

is dependent on how long antimicrobials levels should be kept in patients' serum above the antimicrobial MIC, this is referred to as time-dependent killing and is predicted by T >MIC, β-lactams are an example for this type (**figure 4A**). Concentration-dependent bacterial killing depends solely on the antimicrobial concentration in patients' serum, even if during the rest of dosing interval the antimicrobial serum level is lower than the required MIC, it is predicted by $C_{maximum}$/MIC, an example of this type of bacterial killing are aminoglycosides (**Figure 4B**). Quinolones adopt what is described as mixed concentration-dependency with time-dependency consideration i.e. exposure-dependency, this is predicted by how much of drug is in the patients' serum over time, this predicted by area under the curve divided by MIC i.e. AUC/MIC (**Figure 4C**). (32, 33,) The predicted AUC/MIC for quinolones and respiratory pathogens were determined and clinically correlated with treatment success and microbiological eradication to be somewhere 30-50 for pneumococci, for gram-negative microorganism 125-250, and in the immunocompromized a ratio of at least 100 is required. (32,34) Also mortality was found to become less as we reach above PK/PD break points on treating serious bacterial infections i.e. ≥ 100, and not relying solely on the MIC's of the infecting pathogen. (33)

There have been some debates on whether the free drug area under the curve over minimum inhibitory concentration *ƒ*AUC/MIC or total one should be considered in the interpretation of treatment PK/PD target attainment levels. Quinolones especially the fourth generation quinolones attain PK/PD targets, mostly gemifloxacin, where it attained *ƒ*AUC/MIC of > 100 and total AUC/MIC of over 250. Other respiratory quinolones like moxifloxacin marginally attain the free breakpoint and totally reaches over 150. Levofloxacin 750 mg/day attain the 30 breakpoint, which is the minimum target to attain to have a sizable activity against pneumococci. Clinically, if dosing attain AUC/MIC < 25 or C_{max}/MIC < 3, the clinical success rate reach 57%, AUC/MIC 25-100 or C_{max}/MIC 3-12 the success become 88.5%, while attaining AUC/MIC > 100 or C_{max}/MIC >12 clinical success rise up to 99%, showing a clear evidence of the PK/PD target-attainment application in patients care. (35,36, 37)

Quinolones in Clinical Practice

Quinolones won their reputation due to ease of administration, effectiveness in treating respiratory pathogens and low side effects profile. In a trial of severe pneumococcal pneumonia requiring ICU admission, the goal was to evaluate the outcome of patients with severe CAP, focusing on the impact of levofloxacin versus ofloxacin or ciprofloxacin; either was used with a beta-lactam antibacterial. All pneumococci were penicillin-susceptible. The 15 days survival in CAP patients treated with levofloxacin and beta-lactam were significantly better than the older quinolones ofloxacin or ciprofloxacin and beta-lactams (p = 0.031). (39)

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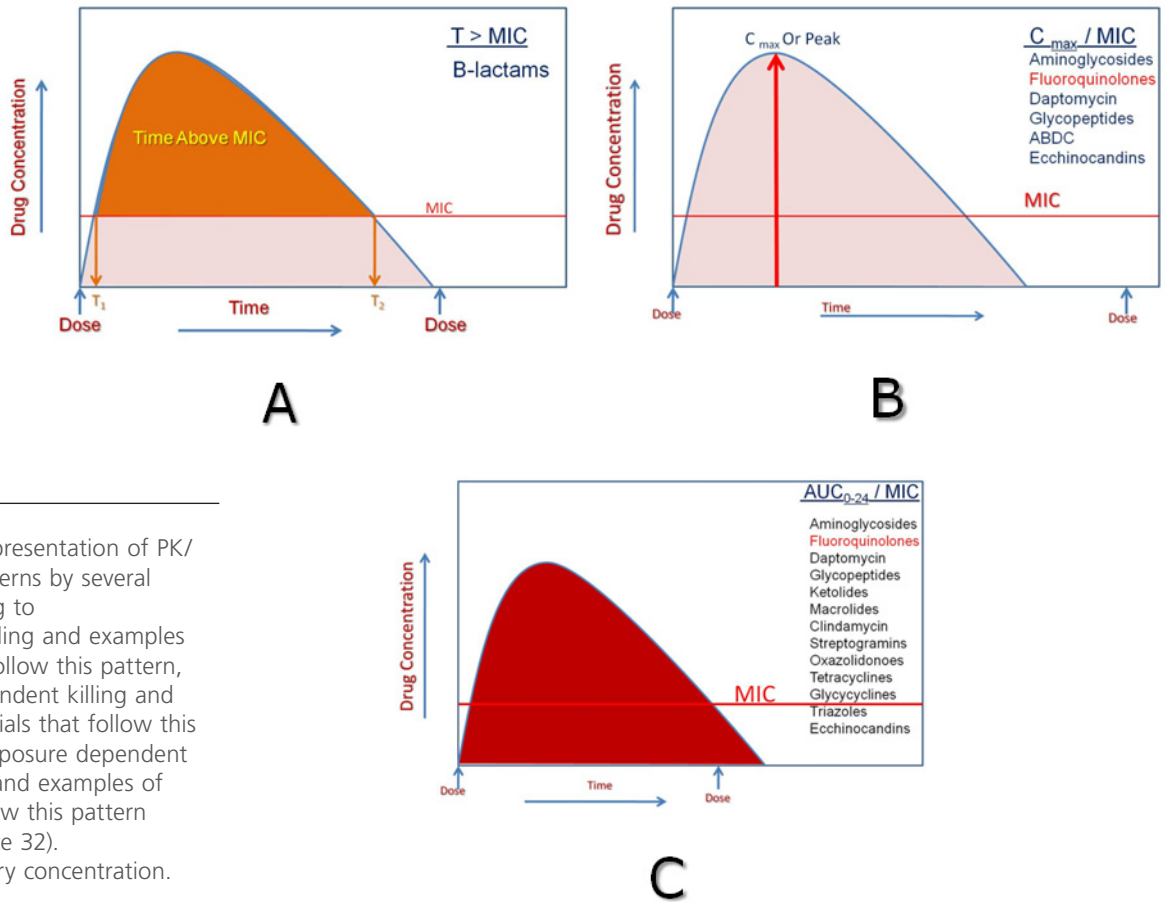

Figure 4. Graphical representation of PK/PD bacterial killing-patterns by several antimicrobials according to (**A**) Time-dependent killing and examples of antimicrobials that follow this pattern, (**B**) Concentration-dependent killing and examples of antimicrobials that follow this pattern, and (**C**) The exposure dependent (Mixed pattern) killing and examples of antimicrobials that follow this pattern (Adapted from reference 32).
MIC: minimum inhibitory concentration.

In another study evaluating recovery and efficacy for moxifloxacin use versus levofloxacin in elderly patients ≥ 65 years old after 5–21 days of completion of therapy. There was no Statistical significant difference in both study arms, whether looking at mild-moderate versus severe CAP, or looking at age group 65 to ≤ 75 years old versus ≥ 75 years old, as tested by P-value and confidence intervals. Nevertheless, there was a significant difference between moxifloxacin and levofloxacin in the speed of recovery in favor of moxifloxacin (p = 0.01), an effect is well appreciated especially in the elderly population with CAP. (40)

Levofloxacin was compared in 750 mg/day dose for 5 days with 500 mg/day for 10 days in the treatment of mild-to-severe CAP. Primary endpoints were clinical efficacy and microbiological efficacy in the clinically evaluable population. The clinical success rates were 92.4% for the 750-mg group and 91.1% for the 500-mg group (95% confidence interval, - 7.0 to 4.4). Microbiologic eradication rates were 93.2% and 92.4% in the 750-mg and 500-mg groups, respectively. Levofloxacin 750 mg/day short course found as effective as 500 mg/day long course, shorter courses and higher doses of levofloxacin may have had accounted better for mutants coverage, with better compliance. (41)

In a randomized multicenter double-blind study including 469 per protocol patients (PPP) split into two arms, gemifloxacin was examined for efficacy and safety, prescribed for 5 and 7 days in the treatment of outpatient mild-moderate CAP. Clinical resolution at follow-up was 95% and 92% for 5 and 7 day treatments respectively (95% CI -1.48 to 7.42), and at the end of therapy was 96% for both regimens (95% CI -3.85 to 3.42). Bacteriological response rates in at the end of therapy were 94% and 96% a t 5 and 7 days regimen respectively (95% CI -8.27 to 3.25) and 91% for both groups at follow-up (95% CI –6.89 to 7.93). Radiological success in PPP at follow-up was 98% and 93% in 5 and 7 day groups respectively (95% CI 0.35, 7.91). Clinical, bacteriological and radiological responses were similar in the 5 and 7 days in the PPP at the end of treatment and follow up assessment endpoints. Side effects were less with the 5 days course, and significantly so with skin rash (p = 0.04). (42). In a meta analysis of randomized controlled trials, LIU You-ning and Falagas et al, evaluated the comparative effectiveness and safety of gemifloxacin when used in CAP and AECB. Gemifloxacin was compared with other quinolones in 5 trials, and compared with β-lactams and/or macrolides in 5 trials, involving 3940 patients. Overall, the treatment success was higher for gemifloxacin when compared with other antibiotics odds

ratio (1.39, 95% CI 1.15 – 1.68) in ITT patients, and (1.33, 1.02–1.73) in clinically evaluable patients. No significant difference was found between gemifloxacin and comparator in microbiological success (1.19, 0.84–1.68) or all-cause mortality (0.82, 0.41–1.63). The total adverse events were similar for gemifloxacin when compared with other quinolones (0.89, 0.56–1.41), while lower when compared with β-lactams and/or macrolides (0.71, 0.57–0.89). Gemifloxacin was associated with fewer cases of diarrhea and more rashes compared with other antibiotics (0.66, 0.48–0.91), and (2.36, 1.18–4.74) respectively. This study suggested that gemifloxacin 320 mg daily is equivalent or superior to other approved antibiotics in effectiveness and safety for CAP and AECB including quinolones comparators i.e. trovafloxacin and levofloxacin. Rash represents potential limitation of gemifloxacin. However, it was found to have similar microbiological response and all-cause mortality like other quinolones. (43)

In an analysis evaluating hospital visits and costs following outpatient treatment of CAP with levofloxacin or moxifloxacin conducted between 2004 -2007, where subsequent 30-day risk of pneumonia-related hospital visits and 30-day health care costs were evaluated, 6352 paired matches were evaluated. Levofloxacin treatment was associated with 35% reduction in the odds of pneumonia-related hospital visits (odds ratio = 0.65, P = 0.004), lower per-patient costs for pneumonia-related hospital visits ($102 vs. $210, P = 0.001), lower pneumonia-related total costs ($363 vs. $491, P < 0.001), and lower total costs ($1308 vs. $1446, P < 0.001). (44) In a similar retrospective analysis, levofloxacin 750 mg/day intravenously versus moxifloxacin 400 mg/day intravenously were used as treatment in patients with CAP for the first 3 of their hospital stay. Levofloxacin-treated patients found to have a shorter mean hospital stay compared with moxifloxacin-treated patients (5.8 vs. 6.4 days; least squares mean difference = 0.54 days; p = 0.020). Hospitalization costs were also lower for the levofloxacin-treated patients (least squares mean difference = US$129; p = 0.753), and complications were similar. (45)

In another retrospective study evaluating intravenous moxifloxacin 400 mg/day and Levofloxacin 750 mg/day, among hospitalized patients with CAP in USA. A comparative analysis of length of stay and total costs as a primary outcome measure, treatment consistency; defined as no additional intravenous moxifloxacin or levofloxacin after ≥1 day off study drug, no switch to another intravenous antibiotic and no addition of another intravenous antibiotic as a secondary outcome measure. In the initial analysis, length of hospital stay and cost was greater with moxifloxacin (p = 0.0001), however on propensity matching analysis, well-matched for demographic, clinical, hospital and payer characteristics, 1300 pair-patients were compared, there was no significant difference in the mean length of hospital stay (p = 0.462) and total cost (p = 0.476). Furthermore, treatment consistency was better with moxifloxacin than levofloxacin before propensity analysis (p = 0.048) and after propensity analysis (p = 0.002). (46)

In conclusion

Penicillin resistant S. pneumoniae should always be considered in the management of CAP, and failing to account for its treatment may have grave consequences. Based on several surveillance studies, RFQ resistance among respiratory pathogens is low and stable so far, lowest for the fourth generation quinolones i.e. gemifloxacin and moxifloxacin. Respiratory pathogens that are resistant to β-lactams and old generation quinolones do not preclude treating them with newer RFQ. As observed in the previous studies the level of resistance is different among various quinolones, and the potential to induce resistance is also different, therefore, quinolones are not equal and should not be used interchangeably. In CAPRIE study, it was demonstrated that the speed of recovery in treating CAP in the elderly occurs faster with the fourth generation quinolones i.e. moxifloxacin compared to the second-generation quinolones i.e. levofloxacin, and when using the fourth-generation for CAP treatment, physicians were more consistent. Cost savings is another point that results from quinolones use in CAP. So far, in bedside medicine, no differences were clearly demonstrated among respiratory quinolones when employed in the treatment of CAP, studies may be needed to further clarify this point. Furthermore, their liberal use have caused some drawbacks like increasing prevalence of MRSA, VRE, quinolone-resistant, ESBL-producing organisms and Clostridium difficile gastrointestinal infection. (47)

Conflict of interest

Jamal Wadi M.D., works as an advisor to HIKMA pharmaceuticals, receives honorarium for consultations, in-services and lectures. Receives honorarium for lectures from Sanofi, Astra-Zeneca and Pfizer. Also receives honorarium from Astra-Zeneca for in-service and consultations, and received a research grant from Astra-Zeneca for another article. Holds no shares for any pharmaceutical company.

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